

Effect of Combined Fluoroquinolone and Azole Use on QT Prolongation in Hematology Patients

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QTc prolongation is a risk factor for development of torsades de pointes (TdP). Combination therapy with fluoroquinolones and azoles is used in patients with hematologic malignancies for prophylaxis and treatment of infection. Both drug classes are implicated as risk factors for QTc prolongation. The cumulative effect on and incidence of QTc prolongation for this combination have not been previously described. A retrospective chart review was performed with hospitalized inpatients from 1 September 2008 to 31 January 2010 comparing QTc interval data from electrocardiogram (ECG) assessment at baseline and after the initiation of combination therapy. Ninety-four patients were eligible for inclusion. The majority, 88 patients (93.6%), received quinolone therapy with levofloxacin. Fifty-three patients (56.4%) received voriconazole; 40 (42.6%) received fluconazole. The overall mean QTc change from baseline was 6.1 (95% confidence interval [CI], 0.2 to 11.9) ms. Twenty-one (22.3%) of the studied patients had clinically significant changes in the QTc while receiving combination fluoroquinolone-azole therapy. Statistically significant risk factors for clinically significant changes in QTc were hypokalemia ($P = 0.03$) and a left-ventricular ejection fraction of $<55\%$ ($P = 0.02$). Low magnesium ($P = 0.11$), exposure to 2 or more drugs with the potential to prolong the QTc interval ($P = 0.17$), and female sex ($P = 0.21$) trended toward significance. Combination therapy with fluoroquinolone and azole antifungals is associated with increased QTc from baseline in hospitalized patients with hematologic malignancies. One in five patients had a clinically significant change in the QTc, warranting close monitoring and risk factor modification to prevent the possibility of further QTc prolongation and risk of TdP.

Combination fluoroquinolone-azole prophylaxis and therapy is common in the hematology patient population. Prophylaxis with these agents has been shown to decrease both bacterial and fungal infections (1–5), and recommendations for use are incorporated as part of the Infectious Diseases Society of America's clinical practice guidelines on the use of antimicrobial agents in neutropenic patients with cancer (6) and the National Comprehensive Cancer Network's guidelines on prevention and treatment of cancer-related infections (7). However, both classes of agents have the potential to prolong the QTc interval and increase the risk for torsades de pointes (TdP) (8–10), with episodes of TdP reported with both azoles and fluoroquinolones (11–19).

The risk of QTc prolongation and TdP in hematology patients on a combination of fluoroquinolone and azole therapy has not been well defined. While it is known that both classes of agents have been associated with QTc prolongation and torsades de pointes, it is not well understood to what degree the combination can increase the QTc interval within this population or whether the combination poses an increased risk of TdP.

The measured QT interval from an electrocardiogram (ECG) is normalized or corrected for a patient's heart rate using a correction formula, and the resulting value is the QTc interval, or simply QTc. A single QTc measurement of >500 ms after initiation of drug therapy has been described as an increased risk factor for a proarrhythmic event, while changes of >30 ms and >60 ms from baseline have also been described (20–24). With a large population of hematology patients who receive both fluoroquinolone and azole prophylaxis and looming concerns about the possibility of increased risk of TdP, our institution initiated a protocol to routinely monitor ECGs in patients who are hospitalized and on both agents concurrently. This study is a retrospective analysis of the ECG measurements that were taken in accordance with our institutional protocol. The study was performed to evaluate the

effect of the combination regimen (fluoroquinolones and azoles) on QTc intervals in the hematology population.

MATERIALS AND METHODS

This study was a retrospective, self-controlled case series evaluation of the effect of fluoroquinolone and azole combination therapy on the QTc interval in hematology patients. We evaluated patients who had electrocardiograms at baseline before combination therapy (ECGs and echocardiograms are usually completed in assessments prior to chemotherapy) and who also had ECGs while on combination therapy. These data were available due to the implementation of an institutional ECG-monitoring protocol prior to study initiation, which called for ECG assessment for patients on combination therapy. The primary aims of this study were (i) to describe the changes in QTc intervals for patients on combination azole and fluoroquinolone therapy and (ii) to determine the number of clinically significant QTc changes after initiating combination therapy. The secondary aims were (i) to identify risk factors associated with clinically significant QTc changes in this population, (ii) to examine the prevalence of cardiology consults related to arrhythmias or QTc concerns while on combination therapy, and (iii) to quantify the need to cease the fluoroquinolone and/or the azole secondary to concerns regarding QTc intervals/arrhythmias. Institutional review board approval was obtained for medical record review. Only patients who gave consent to have their records reviewed for medical studies were included, pursuant to a Minnesota statute.

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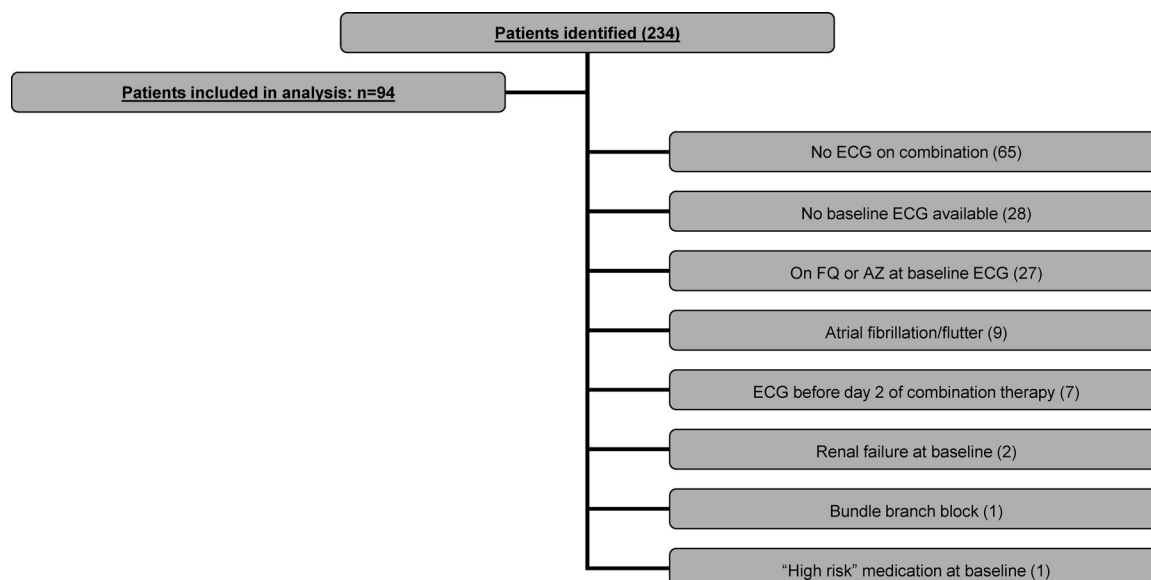


FIG 1 Numbers of patients and applied exclusions. FQ, fluoroquinolone; AZ, azole.

Subjects. All hematology and bone marrow transplant inpatients seen at our institution from 1 October 2008 to 31 January 2010 were eligible for study inclusion. The inclusion criteria included men and women 18 years of age or older, admission to our hospital inpatient hematology or bone marrow transplant service, receipt of combination fluoroquinolone and azole therapy, a baseline ECG within 90 days before starting either fluoroquinolone or azole therapy (if there was more than one ECG in 90 days, the closest to therapy initiation was used), and a follow-up ECG after at least 2 days of combination therapy. Exclusion criteria included patients with atrial fibrillation, a cardiac pacemaker, or bundle branch block; patients on amiodarone or any class III antiarrhythmic; and patients on any drug considered a high risk for TdP at the time of baseline ECG (risk levels are described below). Hospitalized inpatients on our hematology and bone marrow transplant services receiving combination fluoroquinolone and azole therapy were identified through the Computer-Based Antimicrobial Monitoring (CBAM) program used at our medical center. For patients with subsequent admissions (additional rounds of chemotherapy, complications, etc.), patients and data were analyzed for only the first episode where all inclusion criteria were met.

Data collection. For patients who met the inclusion criteria, the following data were obtained from the patient's electronic medical record: QTc assessment by ECG both at baseline and while on combination therapy (our institution uses the GE MAC 5000 or 5500 for assessment of ECGs; the Bazett equation was used for QTc derivation), fluoroquinolone and azole therapy, estimated creatinine clearance, liver function tests (aspartate transaminase [AST], alanine aminotransferase [ALT], and bilirubin), serum magnesium and potassium values (the most recent value within the 24 h prior to the ECG), the most recent ejection fraction assessment via echocardiogram report, other drug therapy with the potential to prolong QTc or invoke TdP either concomitantly or within 8 h prior to the ECG (QTc-prolonging drug therapy was categorized by conditional risk [low], possible risk [medium], and defined risk [high] of TdP, as noted in the risk categories provided online [<http://www.torsades.org>, accessed on 10 September 2010]), whether a cardiology consult was obtained during index admission for purposes related to arrhythmias or QTc prolongation, demographics (age/gender/race), and other risk factors for a prolonged QTc interval or TdP, including (25) a known familial history of long-QT syndrome or sudden cardiac death, history of cardiogenic syncope or long-QT syndrome, heart disease, renal failure (>50% increase in serum creatinine or 50% decrease in estimated creatinine clear-

ance), renal replacement therapy, or hepatic dysfunction (AST, ALT, or bilirubin at >3 times the upper limit of normal). Any adverse outcomes, such as torsades or a need to stop fluoroquinolone and/or azole therapy based on the QTc interval, were documented.

Statistics. The change in QTc was treated as a continuous variable with pretreatment and during-treatment values compared using the paired Students' *t* test. Comparisons were done with baseline and combination ECG measures. In addition, the percentage of patients experiencing a clinically relevant increase in QTc was summarized using a point estimate. Other factors potentially associated with a clinically significant change in the QTc were analyzed via the chi-square or Fisher's exact test (when appropriate) for categorical variables. Descriptive statistics and measures of central tendency, as appropriate for the type and distribution of data collected, were utilized in performing the data analysis. A *P* value of 0.05 was used to define statistical significance for all calculations.

RESULTS

Subjects. Of the 234 patients identified, 94 remained eligible for analysis after inclusions and exclusions were applied (Fig. 1). The mean age of the patients in the sample was 56 years, with a mean follow-up ECG on day 6 of combination therapy. The remaining demographic data are summarized in Table 1. Forty (42.5%) of the included patients were bone marrow transplant patients, the majority of whom were autologous.

Fluoroquinolone and azole use. Table 2 lists the types, distributions, and doses of individual fluoroquinolone and azole use. Of the 94 patients included in the study, 88 (93.6%) received levofloxacin while the remaining 6 (6.4%) received ciprofloxacin. No other fluoroquinolones were noted in our study population. The most common dose of levofloxacin was 500 mg ($n = 66$). In regard to azole use, 53 (56.4%) of the study patients received voriconazole while 40 (42.6%) patients received fluconazole. The majority of patients on voriconazole were on a 200-mg dose ($n = 49$), whereas the majority of fluconazole patients were on a 400-mg dose ($n = 33$). Only 1 patient in this study received posaconazole at 200 mg three times daily. The dosing schedule for the different drugs is not shown, but it should be noted that all of the patients had appropriately ordered intervals based on approved dosing

TABLE 1 Baseline demographic information

Parameter ^a	Value
Age (yr)	56 (±13.7)
Sex [no. (%) male]	56 (59.5)
Wt (kg)	84.2 (±19.6)
BMI (kg/m ²)	29.1 (±6.5)
Race [no. (%)]	
White	80 (85.1)
Black	3 (3.2)
Asian	2 (2.1)
Native American	1 (1.1)
Unknown	8 (8.5)
Autologous BMT (%)	27 (28.7)
Allogeneic BMT (%)	13 (13.8)
Follow-up ECG [days (range)]	6 (2–23)

^a BMI, body mass index; BMT, bone marrow transplant.

schedules and estimated creatinine clearance (where applicable). Table 3 lists the type and frequency of combination fluoroquinolone-azole use. The most common combination was levofloxacin and voriconazole ($n = 50$), while the levofloxacin and fluconazole combination represented 37 patients of the sample.

Concomitant medication with QTc prolongation potential.

The numbers of patients who had exposure to concomitant medication therapy with varying risk potentials for TdP (in addition to their fluoroquinolone and azole combination) are listed in Table 4. None of the study patients had any exposure to a high-risk medication within 8 h prior to a follow-up ECG, while 30 (32%) patients received a low- or medium-risk medication prior to a follow-up ECG. Only 4 (4.3%) patients received two or more medications (in addition to the fluoroquinolone-azole combination) prior to a follow-up ECG. Table 5 lists the medications seen in the study with the potential to prolong QT and/or cause tor-

TABLE 2 Fluoroquinolone-azole use and clinically significant QTc changes by drug and dose

Drug and dose	Clinically significant change [no. (%)]	<i>P</i> value
Fluoroquinolones		
Levofloxacin		
250 mg ($n = 2$)	0 (0)	0.32
500 mg ($n = 66$)	14 (21.2)	
750 mg ($n = 20$)	7 (35)	
Ciprofloxacin		
500 mg ($n = 4$)	0 (0)	1
750 mg ($n = 2$)	0 (0)	
Azoles		
Voriconazole		
200 mg ($n = 49$)	10 (20.4)	0.83
>200 mg ($n = 4$)	1 (25)	
Fluconazole		
100 mg ($n = 3$)	0 (0)	0.58
200 mg ($n = 4$)	1 (25)	
400 mg ($n = 33$)	9 (27.3)	
Posaconazole		
200 mg ($n = 1$)	0 (0)	NA ^a

^a NA, not applicable.

TABLE 3 Fluoroquinolone-azole combinations

Combination	No. of patients (%)
Levofloxacin-voriconazole	50 (53.1)
Levofloxacin-fluconazole	37 (39.4)
Levofloxacin-posaconazole	1 (1)
Ciprofloxacin-voriconazole	3 (3.2)
Ciprofloxacin-fluconazole	3 (3.2)

sades by risk group. The majority of medications were antidepressants, antipsychotics, and antiemetics.

Primary outcomes. Changes in the QTc interval by drug group and episodes of clinical significance are summarized in Table 6. Major clinical significance was defined as a QTc change of >60 ms or a follow-up QTc measurement of >500 ms. Moderate clinical significance was defined as a QTc change of >30 ms and <60 ms or a follow-up QTc of >470 ms (men) or 480 ms (women). For the class combination of fluoroquinolones and azoles, the mean change in QTc from baseline was 6.1 ms (95% confidence interval [CI], 0.2 to 11.9 ms). When examining individual drug combinations, levofloxacin and fluconazole was the only combination to show a statistically significant increase from baseline, with a mean increase of 9.5 ms (95% CI, 2.2 to 16.9 ms).

We also observed 21 (22% [95% CI, 14 to 32%]) clinically significant episodes of QTc prolongation for the class combination. Twenty of these episodes were of moderate clinical significance, with one change of major clinical significance. The number of clinically significant QTc interval changes appeared similar for both combinations of levofloxacin-voriconazole (11 of 50; 22%) and levofloxacin-fluconazole (10 of 37; 27%).

Secondary outcomes. The number of clinically significant QTc changes did not enable us to utilize multivariate analysis. The results of univariate risk factor analysis and the breakdown of the drug dose in relation to clinically significant changes in the QTc are shown in Tables 2 and 7. Higher proportions of patients had increased rates of clinically significant change in the QTc as the doses of levofloxacin, voriconazole, and fluconazole increased. However, the changes in dose did not show a statistically significant effect for any individual drug. Low serum potassium and a left-ventricular ejection fraction (LVEF) of less than 55% demonstrated a statistically significantly increased risk for a clinically significant change in QTc. Low serum magnesium, exposure to 2 or more drugs with potential to prolong the QTc interval, and female sex showed a trend toward increased clinically significant changes in the QTc interval; however, they did not reach statistical significance. Four (4.3%) patients in the study had their azole or fluoroquinolone therapy withheld or discontinued as a result of

TABLE 4 Proportions of patients with exposure to medications with potential to prolong QT and/or cause TdP within 8 h prior to ECG while on combination therapy

Risk group ^a	No. of patients (%)
Low risk	12 (12.8)
Medium risk	22 (23.4)
High risk	0 (0)
Any medication	30 (32.0)
>1 medication ^b	4 (4.3)

^a Risk groups are defined in the text.

^b All exposed to at least 1 low-risk and 1 medium-risk medication.

TABLE 5 Medications with the potential to prolong QT or cause TdP seen in the study population

Drug	Risk group ^a
Amitriptyline	Low
Citalopram	Low
Diphenhydramine	Low
Fluoxetine	Low
Nortriptyline	Low
Sertraline	Low
Sulfamethoxazole/trimethoprim	Low
Tacrolimus	Low
Ondansetron	Medium
Granisetron	Medium
Quetiapine	Medium
Risperidone	Medium
Venlafaxine	Medium
Vardenafil	Medium

^a Risk groups are defined in the text.

QTc prolongation, but there were no cardiology consults for prolonged QTc interval and/or arrhythmia.

DISCUSSION

In our study population, no episodes of TdP were found, though a significant incidence of clinically relevant QTc interval prolongation from baseline was seen after initiation of fluoroquinolone and azole combination therapy. In the study group, 22% of the patients had a clinically significant change in the QTc from baseline after starting combination fluoroquinolone-azole therapy, with hypokalemia and an LVEF of <55% identified as statistically significant risk factors for having a clinically significant change in the QTc. Four patients had therapy withheld or stopped due to changes in the QTc interval.

We found a statistically significant mean increase in the QTc from baseline for the fluoroquinolone-azole class combination, which is not surprising, as the individual classes of drugs have been shown to prolong the QTc interval or cause TdP (8–10, 16). In general, the mean QTc change from baseline in a population is typically utilized in healthy volunteers in early clinical trials to identify the need for further intensive study for drugs that may confer a risk of TdP. Usually, drugs with a mean change of >5 ms under maximum effect may pose a risk for TdP (21). The conditions of our study do not reflect the conditions of premarketing controlled clinical studies investigating maximal drug effect on

the QTc. Nonetheless, we feel that the mean change from baseline of 6.1 ms supports the idea that this combination can significantly prolong the QTc interval and contribute to a risk for TdP.

The levofloxacin-fluconazole combination had a statistically significant mean difference from baseline, while the levofloxacin-voriconazole combination did not. The lack of difference seen may be due in part to low numbers of individual drug combinations. It is also possible that levofloxacin-fluconazole may have had more interactions via cytochrome P450 3A4 (CYP3A4) with concomitant medications that were administered (such as amitriptyline and quetiapine), resulting in the difference. It could also be due to inconsistency in the measured QTc relative to the timing of drug administration, as we would anticipate seeing a greater effect on the QTc if the ECG was assessed closer to a maximum serum concentration. Despite the mean differences between the groups, more importantly, they had comparable percentages (22% and 27%) of clinically significant QTc interval changes, highlighting the fact that both of these combinations are of concern in regard to QTc prolongation potential.

Almost one-quarter of the patients studied had clinically significant changes in the QTc interval while taking combination fluoroquinolone-azole therapy. Our study identified hypokalemia and a low ejection fraction as risk factors for having a clinically significant change in QTc, while female sex, exposure to multiple drugs with the potential to prolong the QTc interval, and low serum magnesium trended toward significance. This is not surprising, given that previous studies have identified all five as risk factors for TdP (25, 26). Regarding electrolyte abnormalities, hypokalemia is thought to reduce the effect of the delayed rectifier potassium channel (I_{Kr}) in cardiac tissue (27), while low magnesium can predispose for TdP because magnesium effectively suppresses the amplitude of early after depolarizations (28) that can lead to TdP.

Patients with hematologic malignancies and bone marrow transplants may be more predisposed to experience QTc prolongation than a general population of hospitalized medical/surgical patients, as the hematology population may more frequently experience hypokalemia and low magnesium due to chemotherapy-associated diarrhea and gastrointestinal involvement of graft-versus-host disease. Additionally, this population receives cardiotoxic chemotherapy and may be more predisposed to a reduced ejection fraction. These factors may have contributed to a higher frequency of events in our study population, and the same prevalence of clinically significant QTc interval prolongation

TABLE 6 QTc interval data for antimicrobial class combinations and individual drug combinations of fluoroquinolones and azoles

Combination ^a	Baseline QTc ^b (ms)	Follow-up QTc ^b (ms)	QTc change ^c (ms)	Clinically significant change ^d	
				Moderate	Major
AZ-FQ (<i>n</i> = 94)	436.6 (20.9)	442.7 (26.6)	+6.1 (0.2–11.9)	20	1
Lev-Vor (<i>n</i> = 50)	439.3 (20.0)	444.5 (29.4)	+5.2 (–4.0–14.5)	10	1
Lev-Flu (<i>n</i> = 37)	431.4 (20.3)	440.9 (25.0)	+9.5 (2.2–16.9)	10	0
Lev-Pos (<i>n</i> = 1)	447	423	–24	0	0
Cip-Vor (<i>n</i> = 3)	436.7 (6.1)	447.0 (11.4)	+10.3 (–7.3–28.0)	0	0
Cip-Flu (<i>n</i> = 3)	453.0 (44.7)	436.0 (6.0)	–17.0 (–120.1–86.1)	0	0

^a AZ, azole; FQ, fluoroquinolone; Lev, levofloxacin; Cip, ciprofloxacin; Vor, voriconazole; Flu, fluconazole; Pos, posaconazole.

^b Mean change (standard deviation).

^c The 95% CI is in parentheses.

^d Number of events.

TABLE 7 Univariate risk factor comparison

Risk factor ^a	Clinically significant change [no. of events (%)]	P value
Hemodialysis, CRRT, or ARF		
Yes (<i>n</i> = 7)	2 (28.5)	0.68
No (<i>n</i> = 87)	19 (21.8)	
Additional QT-prolonging medication within 8 h prior to ECG		
Yes (<i>n</i> = 30)	8 (26.7)	0.49
No (<i>n</i> = 64)	13 (20.3)	
2 or more QT-prolonging medications within 8 h prior to ECG		
Yes (<i>n</i> = 4)	2 (50.0)	0.17
No (<i>n</i> = 90)	19 (21.1)	
Heart disease		
Yes (<i>n</i> = 14)	4 (28.5)	0.54
No (<i>n</i> = 80)	17 (21.2)	
Age > 65 yr		
Yes (<i>n</i> = 29)	6 (20.7)	0.79
No (<i>n</i> = 65)	15 (23.8)	
Sex		
Female (<i>n</i> = 38)	11 (28.9)	0.21
Male (<i>n</i> = 56)	10 (17.8)	
Hypokalemia (<i>K</i> < 3.6)		
Yes (<i>n</i> = 23)	9 (39.3)	0.03
No (<i>n</i> = 71)	12 (16.9)	
Low serum magnesium (<i>Mg</i> < 1.7)		
Yes (<i>n</i> = 9)	4 (44.4)	0.11
No (<i>n</i> = 73)	15 (20.5)	
Liver function tests > 3 × ULN ^b		
Yes (<i>n</i> = 7)	1 (14.3)	0.59
No (<i>n</i> = 87)	20 (23.0)	
Ejection fraction < 55%		
Yes (<i>n</i> = 11)	5 (45.5)	0.02
No (<i>n</i> = 75)	12 (16.0)	

^a CRRT, continuous renal replacement therapy; ARF, acute renal failure.

^b Liver function tests were serum alanine aminotransferase, aspartate aminotransferase, and bilirubin; ULN, upper limit of normal.

might not be seen in a different patient population receiving fluoroquinolone-azole combination therapy. Indeed, given the incidence of these nonantimicrobial risk factors for QTc interval prolongation (electrolyte abnormalities and cardiotoxic chemotherapy) in patients receiving chemotherapy for hematologic malignancies or those receiving hematopoietic stem cell transplantation, we recommend that such patients on combination fluoroquinolone-azole therapy receive appropriate clinical and ECG monitoring.

A statistically significant effect in relation to drug dose and clinically significant QTc change was not seen in our population. This is likely due to the low event rate and low numbers for groups receiving different doses. Nonetheless, the trend toward increasing prevalence of clinically significant QTc changes for increasing doses of levofloxacin, voriconazole, and fluconazole is not surprising. In general, QTc prolongation and the risk for TdP will increase as the concentration of drug increases (25). This is due to

the effect of higher drug levels increasingly enhancing the blockade of the delayed rectifier potassium channel in cardiac tissue (I_{Kr}) or providing a greater effect on inhibition of the metabolic pathways of other drugs that can block the channel. With higher drug doses administered, consequent higher drug levels should be seen. However, serum concentrations are variable per patient based on the drug volume of distribution and patient-specific drug clearance. Additionally, the timing of QTc assessment in relation to the dosing interval has an effect (e.g., a QTc assessed at the serum peak level would be expected to be greater than one drawn at a serum trough level). Serum levels are not typically utilized clinically for the fluoroquinolones, and while voriconazole levels can be used in the clinical setting, none of our included patients had voriconazole levels ascertained. This is not surprising, because the majority of patients in this population are on voriconazole as a prophylactic agent, and voriconazole levels are not routinely performed in patients on prophylaxis unless clinical toxicity is suspected. Nonetheless, despite the lack of demonstrated dose effect in this study, we feel that providers should be aware that higher doses of quinolones and azoles could potentially have a greater effect on the QTc.

To our knowledge, this is the first study examining the QTc prolongation effects of azole and fluoroquinolone combination therapy. While the QTc interval is an imperfect surrogate for assessing the risk for TdP (25, 26), it is commonly used in the clinical setting to determine the risk for possible arrhythmia, and it has been shown that a drug-induced QTc of >500 ms increases the risk for TdP (20, 23, 24). Unfortunately, there is not a well-defined, graduated definition for the degree of clinical severity in regard to QTc change after drug administration. The American Heart Association/American College of Cardiology (AHA/ACC) consensus statement on prevention of TdP in hospital settings has recommended prompt response with risk factor modification and alternate pharmacotherapy when the QTc exceeds 500 ms or is increased by >60 ms from the predrug baseline (25), which is why we felt that these criteria would be effectively deemed a change of major clinical significance. While our definitions of moderate clinical significance are below these thresholds, the AHA/ACC consensus statement also notes that QTcs of >470 ms (males) and >480 ms (females) are considered to be greater than the 99th percentile for their respective populations. Additionally, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) harmonized tripartite guideline for the clinical evaluation of the QT-QTc interval prolongation and proarrhythmic potentials of nonantiarrhythmic drugs identifies a change of >30 ms from baseline as cause for concern (21). We feel that both circumstances, while they do not meet the criteria for major clinical significance, still represent a situation in which the patient's "repolarization reserve" has been compromised (29). With a QTc change of moderate clinical significance, we feel that further risk factors could occur in a hospital environment that could increase the opportunity for an event of torsades and should warrant close monitoring.

At our institution, we perform routine ECGs in our hematology and transplant patients receiving combination fluoroquinolone-azole therapy. Our finding that 22% of patients experienced clinically significant changes from baseline highlights the importance of clinical monitoring and early identification of modifiable risk factors (concurrent prodysrhythmic medications, electrolyte

abnormalities, etc.) to reduce the risk of further QTc prolongation and development of TdP. In our study, clinical ECG monitoring resulted in holding or discontinuing fluoroquinolone-azole therapy in 4.3% of patients, which suggests it is an important prompt for clinicians to acknowledge the importance of QTc prolongation.

The study was limited due to the fact that we were assessing a surrogate marker of torsades rather than events of torsades themselves, though the rarity of events would make this extremely challenging. The low number of QTc prolongation events in the study likely made it difficult to see a statistically significant effect of gender, multiple drugs with the potential to prolong the QTc interval, low magnesium, and different drug doses. It is also possible that additional medications with the potential to prolong the QT interval were not administered in a time frame that would have enabled detection of the effect, which would be highly dependent on the half-life, organ clearance, dose administration in relation to ECG assessment, etc. The risk contributed is highly variable for each drug, and having low numbers of individual drugs in the collective risk factor analysis may have made it difficult to see a more pronounced drug effect. Additionally, we did not have serum concentrations available for the drugs we were assessing. The study is also limited by its retrospective nature. As a retrospective study, many variables could not be controlled, such as the uniformity of ECG assessment in relation to the time of day and time relative to drug doses. Some patients may have had ECGs ascertained for purposes other than QTc interval assessment, which could have introduced some selection bias. Due to low numbers of clinically significant events for each drug combination, interpretation of risk factors for each combination and use of multivariate methods for risk assessment were not feasible.

Conclusions. Our study demonstrates that the combination of a fluoroquinolone and an azole antifungal is associated with an increased QTc interval from baseline in hospitalized hematology and bone marrow transplant patients. Almost 25% of the patients were identified as having a clinically significant QTc interval change that could lead to TdP. We feel that ECG assessment after starting combination fluoroquinolone-azole therapy in this particular patient population should be considered if other contributing QTc prolongation factors are commonly present as well, including hypokalemia and cardiomyopathy. Certainly larger randomized studies examining individual drug combinations while controlling confounding factors would help to elucidate the true risk of torsades and better quantify the effect on the QTc interval.

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